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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/988,013	11/16/2001	Shui-on Leung	IMMU:014US2	7681

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EXAMINER
BLANCHARD, DAVID J

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
08/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/988,013	LEUNG ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-32 and 38-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-32 and 38-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-27 and 33-37 are cancelled.

Claims 40-43 have been added.

2. Claims 28-32 and 38-43 are pending and under consideration.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

Objections/Rejections Maintained and New Grounds of Rejections

5. The oath or declaration is defective because the present application is a continuation-in-part based on the lack of adequate written description (see item no. 6 below) is maintained.

The reply filed 6/14/2007 states that the present application is a continuation and entitled to the priority date of USSN 08/892,576 and a new oath or declaration is not required. This has been fully considered but is not found persuasive. The examiner maintains that the present application does not provide adequate written description for the claimed subject matter (see item no.). A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01, 602.02 and See 37 CFR 1.63(d).

The oath or declaration is defective because: A newly executed oath or declaration must be filed in any continuation-in-part application (see amendment to the specification filed 6/30/05), which application may name all, more, or fewer than all of the inventors named in the prior application. See 37 CFR 1.63(d).

6. The rejection of claims 28-32, 38-39 and now applied to newly added claims 40-43 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description

requirement is maintained. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In the reply filed 6/14/2007, Applicant reviews the case law cited by the examiner in the previous Office Action. Applicant states that the instant claims are distinguished from the cited case law in that the present claims are drawn to a method and not a product. Applicants' arguments have been fully considered but are not found persuasive because it is irrelevant that the present claims are drawn to a method, the statute applied to all types of inventions. Rochester also attempts to distinguish *Fiers*, *Lilly*, and *Enzo* by suggesting that the holdings in those cases were limited to composition of matter claims, whereas the '850 patent is directed to a method. We agree with the district court that that is "a semantic distinction without a difference." *Univ. of Rochester*, 249 F. Supp. 2d at 228. Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods.

Applicant argues that the original specification clearly informs a person of ordinary skill in the art that applicant possessed a method for humanizing antibodies in which each framework region (FR) sequence of a non-human antibody to determine the degree of sequence homology between the non-human antibody FRs and the human antibody FRs, and then each FR in the non-human antibody is replaced with a human antibody FR which exhibits sequence homology to the non-human antibody FRs and applicant points to the following disclosure in the specification:

> By comparing the murine variable (V) region framework (FR) sequences of LL2 to that of human antibodies in the Kabat database (Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th ed., U.S. Department of Health and Human Services, U.S. Government Printing Office, Washington, D.C.), which is incorporated by reference, the human REI (FIG. 1A, SEQ ID NO. 6) and EU (FIG. 1B, SEQ ID NOS. 9 and 8) sequences were found to

> exhibit the highest degree of sequence homology to the FRs of VK and VH domains of LL2, respectively. Therefore, the REI and EU FRs were selected as the human frameworks onto which the CDRs for LL2 VK and VH were grafted, respectively. The FR4 sequence of NEWM, however, rather than that of EU, was used to replace the EU FR4 sequence for the humanization of LL2 heavy chain. Based on the results of computer modeling studies (FIGS. 2A and 2B), murine FR residues having potential CDR contacts, which might affect the affinity and specificity of the resultant antibody, were retained in the design of the humanized FR sequences (FIG. 1).

Based on the disclosure, applicant concludes that each framework sequence was compared to its corresponding framework region in a database of human antibodies and that replacement of framework regions was based on sequence homology. Applicants' arguments have been fully considered but are not found persuasive. It is reiterated that the specification as filed only discloses a single monoclonal antibody LL2, which was humanized according to the claimed method in which the LL2 CDRs of the light chain were grafted onto human REI frameworks and the heavy chain CDRs were grafted onto the human EU frameworks, except for FR4, which was from the human NEWM antibody. Applicant's reliance on a single disclosed species is insufficient to support the broader scope of the claims encompassing multiple subgenera because there is insufficient disclosure of a "representative number of species" and there is substantial variation within the subgenera claimed. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004) ("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of

any species other than the one disclosed." *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). For example, according to Gorman et al the largest unknown variable when reshaping an antibody is the selection of the human immunoglobulin variable region from which the framework sequences are derived because the framework regions hold the CDRs in their correct spatial orientation and can sometimes even participate in antigen binding. At present, there are insufficient published reshaping results to generalize a "best framework" selection strategy (Gorman et al. Proc. Natl. Acad. Sci, USA, 88:4181-4185, May 1991, particularly pg. 4182, 2nd col.). There is no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other CDRs other than the LL2 are suitable for grafting onto the human REI light chain frameworks and onto the human EU and NEWM heavy chain frameworks. Further, in contrast to the scope of the claims, Applicant's disclose that the human frameworks are selected based on the highest degree of sequence homology to the murine variable region sequences. While there may be a general method of selecting the most homologous frameworks for humanizing a given monoclonal antibody, applicants' priority documents only provide adequate written support for the humanization of murine monoclonal antibody LL2 wherein the light chain frameworks are from the human REI antibody and the heavy chain frameworks for FR1-FR3 are from the human EU antibody and heavy chain FR4 is from the human NEWM antibody. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith* 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05. One of skill in the art would not recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the multiple subgenera of the claimed method in view of the single disclosed species.

With respect to newly added claims 40-43 and as previously established on the record, the disclosure of Example 1 and Figure 1 in which the human EU heavy chain framework regions and the human REI light chain framework regions are selected based on having the highest sequence homology does not provide adequate written support for the broader limitation of the present claims, which encompasses the

selection of each heavy chain framework region (i.e., FR1, FR2, FR3 and FR4) from at least one human antibody and the selection of each light chain framework region (i.e., FR1, FR2, FR3 and FR4) from at least one human antibody, which broadly embraces selecting heavy chain framework regions from four different human antibodies and selecting light chain framework regions from four different human antibodies. The selection of all four framework regions of the light chain (i.e., FR1, FR2, FR3 and FR4) from a single human antibody, REI, does not provide sufficient written support for the broader features and limitations of the present claims, inclusive to selecting each of FR1, FR2, FR3 and FR4 from different human antibodies. Further, while the as filed specification discloses the human EU framework regions were used for the humanized antibody with the exception that human NEWM was selected for FR4, this does not provide adequate written description for the selection of three or all four heavy chain framework regions (i.e., FR1, FR2, FR3 and FR4) from different human antibodies. Further, the disclosure that the selection of the human NEWM for FR4 of the heavy chain was due to lack of X-ray coordinate data for the EU sequence does not provide sufficient direction and guidance to the currently claimed limitations, i.e., the selection of three or all four heavy chain framework regions (i.e., FR1, FR2, FR3 and FR4) from different human antibodies. Applicants' reliance on the use of the REI human frameworks for the humanized light chain variable region and the use of the human EU FR1-3 regions and the human NEWM FR4 for the humanized heavy chain variable region for adequate written support for the limitations "replacing each FR in the non-human antibody with a human antibody FR which exhibits sequence homology to the non-human antibody FRs", does not provide adequate written support for using the FR1, FR2, FR3 and FR4 from four different human antibodies for each of the light and heavy chain variable domains. For example, there is no disclosure of a method for producing humanized antibodies wherein the heavy chain variable domain comprises a human EU FR1, a human Gal FR2, a human Jon FR3 and a human NEW FR4 and wherein each light chain FR (i.e., FR1, FR2, FR3 and FR4) is selected from different human FRs having the highest homology as embraced by the currently claimed limitations.

Applicants' arguments of the disclosure of other antibodies by the presently claimed method wherein the disclosure is found in different applications is acknowledged, but is not found persuasive. Compliance with the written description requirement of the first paragraph of 35 U.S.C 112 is based upon the written description of the present application. Further, while the method may be enabled as it pertains to other antibodies, applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991). An invention may be enabled even though it has not been described. See, e.g., *In re DiLeone*, 436 F.2d 1404, 1405, 168 USPQ 592 (CCPA 1971) ("[I]t is possible for a specification to enable the practice of an invention as broadly as it is claimed, and still not describe that invention.").

Therefore, the instant claims now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the instant claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in the instant claims in the specification or claims, as filed, or remove these limitations from the claims in response to this Office Action.

Priority

7. The disclosure of the prior-filed application, USSN 08/820,576 with which applicant argues, does not to provide adequate support in the manner provided by the first paragraph of 35 U.S.C. 112 for the present claims (see item no. 6 above).

The later-filed application must be an application for a patent for an invention, which is also disclosed, in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the

requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

8. The rejection of claims 28-32, 38-39 and now applied to newly added claims 40-43 under 35 U.S.C. 102(b) as being anticipated by Leung et al [a] (US Patent 5,789,554, issued 8/4/1998, IDS reference A2 filed 4/30/2002) is maintained.

The response filed 6/14/2007 states that the instant application is a continuation of USSN 09/741,843, filed 12/22/00, which was a continuation of USSN 09/127,902, filed 8/3/98 (now U.S. Patent No. 6,187,287), which was a continuation of USSN 08/690,102, filed 7/31/96 (now U.S. Patent No. 5,789,554), which was a continuation of USSN 08/289,576, filed 8/12/94. Support for the instant claimed subject matter may be found going back to the original priority document, USSN 08/280,576, filed 8/12/94, as detailed below in response to the written description rejection. Applicants' arguments have been fully considered but are not found persuasive. The disclosure of the prior-filed application, USSN 08/820,576 with which applicant argues, does not to provide adequate support in the manner provided by the first paragraph of 35 U.S.C. 112 for the presently claimed subject matter as discussed supra (see item no. 6 above).

For these reasons the rejection of claims 28-32 and 38-43 under 35 U.S.C. 102(b) as being anticipated by Leung et al [a] is maintained.

9. The rejection of claims 28-32 and now applied to newly added claims 38-39 under 35 U.S.C. 102(b) as being anticipated by Leung et al [b] (Molecular immunology, 32(17-18):1413-1427, 1995, cited on PTO-892 mailed 2/20/2004) is maintained.

Applicant argues as above against Leung et al [a] and the examiners' remarks above apply here as well and as such the rejection of claims 28-32 and 38-43 under 35 U.S.C. 102(b) as being anticipated by Leung et al [b] is maintained.

10. No claims are allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643